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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/803,918	DAYER ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-61* is/are pending in the application.

4a) Of the above claim(s) *1-8,11-14,18-35,44,45 and 50-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10,15,16,36-43 and 46-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/24/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-16, and 18-61 are pending.

2. Claims 1-8, 11-14, 18-35, 44-45, and 50-61 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. Claims 9-10, 15-16, 36-43, and 46-49 are being acted upon in this Office Action.

4. In view of the amendment filed 9/24/04, the following rejection remains.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 9-10, 15-16, 36-43 and 46-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for

(1) a process for making an apo-A-I fragment T-ell activation inhibitor-like polypeptide fragment comprising culturing a eukaryotic cell comprising a vector comprising a nucleic acid molecule *consisting of* a nucleotide sequence selected from: (a) a nucleotide sequence as set forth in residues 73 to 582 in SEQ ID NO: 1; (b) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 194 in SEQ ID NO: 2; (c) a nucleotide sequence as set forth in residues 73 to 432 in SEQ ID NO: 1; (d) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 144 in SEQ ID NO: 2; (e) a nucleotide sequence as set forth in residues 466 to 801 in SEQ ID NO : 1; (f) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 113 in SEQ ID NO: 2; (g) a nucleotide sequence encoding the polypeptide as set forth in residues 73 to 113 in SEQ ID NO: 2; (h) a nucleotide sequence encoding the polypeptide as set forth in residues 156 to 267 in SEQ ID NO: 2; and (i) a nucleotide sequence complementary to at least one of (a)-(h) wherein a culture condition suitable for expressing the polypeptide is selected and the polypeptide is isolated from the culture;

(2) a process for making an apo-A-I fragment T-ell activation inhibitor-like polypeptide fragment comprising culturing a prokaryotic cell comprising a vector comprising a nucleic acid

molecule *consisting of* a nucleotide sequence selected from: (a) a nucleotide sequence as set forth in residues 73 to 582 in SEQ ID NO: 1; (b) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 194 in SEQ ID NO: 2; (c) a nucleotide sequence as set forth in residues 73 to 432 in SEQ ID NO: 1; (d) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 144 in SEQ ID NO: 2; (e) a nucleotide sequence as set forth in residues 466 to 801 in SEQ ID NO : 1; (f) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 113 in SEQ ID NO: 2; (g) a nucleotide sequence encoding the polypeptide as set forth in residues 73 to 113 in SEQ ID NO: 2; (h) a nucleotide sequence encoding the polypeptide as set forth in residues 156 to 267 in SEQ ID NO: 2; and (i) a nucleotide sequence complementary to at least one of (a)-(h) wherein a culture condition suitable for expressing the polypeptide is selected and the polypeptide is isolated from the culture;

(3) an isolated apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment consisting of an amino acid sequence selected from: (a) an amino acid sequence as set forth in residues 25 to 194 of SEQ ID NO:2 ; (b) an amino acid sequence as set forth in residues 25 to 144 of SEQ ID NO: 2; (c) an amino acid sequence as set forth in residues 156 to 267 of SEQ ID NO: 2; (d) an amino acid sequence as set forth in residues 25 to 113 of SEQ ID NO: 2; and (e) an amino acid sequence as set forth in residues 73 to 113 of SEQ ID NO:2;

(4) an isolated apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment encoded by a nucleic acid molecule consisting of a nucleotide sequence selected from: (1) a nucleotide sequence as set forth in residues 73 to 582 in SEQ ID NO : 1; (2) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 194 in SEQ ID NO:2; (3) a nucleotide sequence as set forth in residues 73 to 432 in SEQ ID NO: 1; (4) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 144 in SEQ ID NO: 2; (5) the nucleotide sequence as set forth in residues 466 to 801 in SEQ ID NO: 1; (6) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 113 in SEQ ID NO: 2; (7) a nucleotide sequence encoding the polypeptide as set forth in residues 73 to 113 in SEQ ID NO: 2; (8) a nucleotide sequence encoding the polypeptide as set forth in residues 156 to 267 in SEQ ID NO: 2; wherein the nucleotide sequence encodes a polypeptide that inhibits tumor necrosis factor (TNF) or interleukin-l (IL-1) production by monocytes;

(5) a composition comprising the polypeptide mentioned above and a pharmaceutically acceptable formulation agent such as a carrier, adjuvant, solubilizer, stabilizer or anti-oxidant and

(6) the polypeptide mentioned above which is covalently modified with a soluble polymer such as the ones set forth in claims 40-43; and

(7) a fusion polypeptide comprising the polypeptide mentioned above and a heterologous amino acid sequence selected from an IgG constant domain or fragment thereof, an alkaline phosphatase a tat protein or a FLAG epitope for detection assays, **does not** reasonable provided enablement for a process for making an apo-A-I fragment T-ell activation inhibitor-like polypeptide fragment comprising culturing a eukaryotic cell comprising a vector comprising a nucleic acid molecule *consisting essentially of* any nucleotide sequence as set forth in claims 9 and 10, any nucleotide sequence encoding any polypeptide as set forth in (a) through (h) having one or more conservative amino acid substitutions wherein the polypeptide inhibits tumor necrosis factor (TNF) or interleukin-1 (IL-1) production by monocytes as set forth in claims 9 and 10, (2) any isolated apo-A-I fragment T-cell activation inhibitor like polypeptide fragment "consisting essentially of" any amino acid sequence as set forth in claims 15, any amino acid sequence as set forth in (a) to (e) having one or more conservative amino acid substitutions wherein the polypeptide inhibits tumor necrosis factor (TNF) or interleukin-1 (IL-1) production by monocytes, (3) any isolated apo-A-I fragment T-cell activation inhibitor like polypeptide fragment encoded by a nucleic acid molecule consisting essentially of any nucleotide sequence as set forth in claim 16, such as any nucleotide sequence encoding as set forth in claim 16 having any one or more conservative amino acid substitutions for regulates T-cell-mediated activation of monocytes, (4) any polypeptide mentioned above is covalently modified (claims 40-43), (4) any composition comprising any apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment as set forth in claims 36-39 for treating any disease, and (5) any fusion polypeptide comprising any apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment and a heterologous amino acid sequence selected from an IgG constant domain, any fragment thereof, an alkaline phosphatase, or any "fragment thereof", a tat protein or a FLAG epitope (claims 46-49) for any purpose. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims for the same reasons set forth in Paper No 13.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working

examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only human Apo-A-I comprising SEQ ID NO: 2 encoding by the polynucleotide of SEQ ID NO: 1. Only the human Apo-A1 fragment recovering from the fractions 23-26 with a molecular weight 28 kDa protein consisting of amino acid residues 25 to 194 of SEQ ID NO: 2 has inhibitory activity of T cell signaling of monocyte for IL-1β and TNFα production in vitro (See p7, Figure 4A-B).

The specification does not teach how to make all apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment "consisting essentially of" any amino acid sequence or nucleotide sequence set forth in claims 9-10, 15-16, 36-43 and 46-49 because the term "consisting essentially of" is open-ended. It expands the fragment to include additional amino acids, the corresponding nucleic acids at either or both ends. There is inadequate guidance as to which amino acids and/or nucleic acids to be added and whether the resulting fragment maintains its structure and function. Further, the specification as filed does not teach which amino acids within (a) the amino acid sequence as set forth in residues 25 to 194 of SEQ ID NO: 2; (b) an amino acid sequence as set forth in residues 25 to 144 of SEQ ID NO: 2; (c) an amino acid sequence as set forth in residues 156 to 267 of SEQ ID NO: 2; (d) an amino acid sequence as set forth in residues 25 to 113 of SEQ ID NO: 2; (e) an amino acid sequence as set forth in residues 73 to 113 of SEQ ID NO: 2 to be substitute and whether the resulting "one or more substitution" maintains its structure and function. Likewise, the specification dose not teach which nucleotides within the nucleic acid sequence selected from: (1) a nucleotide sequence as set forth in residues 73 to 582 in SEQ ID NO: 1; (2) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 194 in SEQ ID NO:2; (3) a nucleotide sequence as set forth in residues 73 to 432 in SEQ ID NO: 1; (4) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 144 in SEQ ID NO: 2; (5) the nucleotide sequence as set forth in residues 466 to 801 in SEQ ID NO: 1; (6) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 113 in SEQ ID NO: 2; (7) a nucleotide sequence encoding the polypeptide as set forth in residues 73 to 113 in SEQ ID NO: 2; (8) a nucleotide sequence encoding the polypeptide as set forth in residues 156 to 267 in SEQ ID NO: 2 to be substitute and whether the resulting nucleotide sequence having "one or more substitutions" encodes a polypeptide that inhibits tumor necrosis factor (TNF) or

interleukin-l (IL-1) production by monocytes. There is insufficient guidance as to the structure of any apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment without the amino acid sequence or the corresponding nucleotide sequence.

The problem of predicting functional aspects of the product from mere sequence data of a single nucleic acid sequence and what changes can be tolerated is complex and well outside the realm of routine experimentation. *In re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Without such guidance, the fragments which can be made and used to encode peptides of the claimed activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue. See *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

Attwood *et al*, of record, teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable.

Skolnick *et al*, of record, teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire document, Abstract in particular).

It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama *et al*, teach that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (Figure 1 in particular). Yet, Mikayama *et al*, of record, teach further that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF bioactivity (Abstract in particular). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Given the unlimited number of apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment having one or more substitutions, there is insufficient working example demonstrating that any apoA-I fragment is effective for inhibiting T-cell activation via inhibition of TNF alpha and/or IL-1 production by monocytes. Given the unlimited number of apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment having one or more substitutions, it is unpredictable which undisclosed apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment inhibits TNF production

by monocytes, which fragment inhibits IL-1 production or both by monocytes. Until the structure of the specific fragment having the specific function has been identified, the specification as filed merely extends an invention for one skill in the art for further experimentation to arrive at the claimed invention.

Since the amino acid sequence of the apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment, the corresponding nucleotide sequence mentioned above are not enabled, it follows that any composition comprising any undisclosed apo-A-fragment for treating all disease is not enabled. It also follows that all undisclosed apo-A-I fragment which is covalently modified (claims 40-43) are not enabled. Given the lack of guidance as to the structure and function of any undisclosed the apo-A-fragment, the fusion polypeptide comprising said undisclosed apo-A-I fragment to any IgG constant domain, any fragment of alkaline phosphatase, tat protein and FlAG epitope is not enabled. Further, there is insufficient guidance as to which "fragment thereof" of IgG constant or alkaline phosphatase the undisclosed apo-A-I fragment fused to.

Even if the apo-A-fragment limited to the 28 kDa protein consisting of amino acid residues 25 to 194 of SEQ ID NO: 2, there is no in vivo working example that the claimed apo-A-I fragment could treat any disease. A pharmaceutical composition (claims 36-39) in the absence of in vivo data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the polypeptide fragment unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

For these reasons, it would require undue experimentation even for one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of

the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 9/24/04 have been fully considered but are not found persuasive.

Applicants' position is that the phrase "consisting essentially of " is not open-ended like the phrase "comprising". The claims encompass only sequences that do not materially affect the basic and novel characteristics of the claimed AFTI polypeptide fragments. Claims 9, 10, 15 and 16 have been amended.

However, there is insufficient guidance as to the structure of any apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment having one or more conservative substitution without the amino acid sequence and/or the corresponding nucleotide sequence. Further, the term "consisting essentially of" is still open-ended, albeit the sequence is not the same length as set forth in SEQ ID NO: 2. There is insufficient guidance as to which amino acids to be added to the fragment, and the corresponding nucleotides. Applicants are directed to the detailed rejection discussed supra.

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone

are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

10. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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